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Good practices for Abbreviated Impaction Measurements (AIM) in dry powder inhalers (DPIs)

Specific recommendations when implementing AIM in the laboratory

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On behalf of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)

Introduction

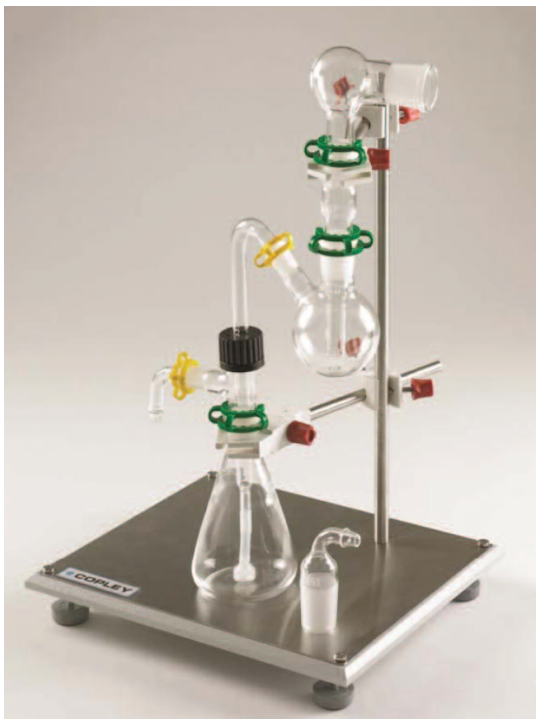
In the past five years, the concept of abbreviated impaction measurements (AIM) has been developed collaboratively by individual companies, as well as through industry groups such as the European Pharmaceutical Aerosol Group (EPAG) and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The main stimulus for developing AIM concepts was the need to find improvements to the very labor intensive, time consuming and complex methods of acquiring aerodynamic particle size distribution (APSD)-related measures using the compendial full resolution cascade impaction (CI) apparatuses. A range of AIM equipment is now available for use (Figures 1-5), and detailed descriptions of their construction and use have been reported.[1] There are AIM systems based on Andersen viable[2] and non-viable[3] impactors, as well as options for working with so-called reduced Next Generation Pharmaceutical Impactors (rNGIs)[4, 5] and the Fast Screening Impactor (FSI), which was developed from technology already in place associated with the pre-separator of the NGI.[6] Initial benefits to the industry could involve implementation of AIM during the early-phase screening of respiratory products.

In 2010, EPAG led a series of experiments that were reported as part of a Drug Delivery to the Lungs-21 conference workshop. Those experiments identified several factors that should be considered when setting up AIM-based measurements for the first time.[7] Subsequent experimental studies, many of which have been referenced by Tougas, et al.,[1] have set out in some detail the best practices for AIM testing of orally inhaled products (OIPs). The availability of such best practices and their consistent application by all practitioners should facilitate the ultimate acceptance of AIM techniques by compendial and regulatory authorities.

The present article provides a summary of the current best practices for AIM testing of orally inhaled products, with a focus on dry powder inhalers (DPIs), which are of particular interest to many developers as well as regulators. In addition, this

Figure 1

Twin impinger; an early attempt at AIM-based measurements.



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article builds on these best practices with the intention of providing counsel to those considering the implementation of an AIM-based measurement program for DPIs. The advice should therefore be considered as a whole in relation to the body of experimental and theoretical work already published. Furthermore, there are aspects that could well have application for the assessment of other forms of orally inhaled products, but the focus of these considerations is specifically for DPIs.

General practices

Bonam, et al.[8] identified the risk of an erroneous measurement arising from the traditional full resolution CI approach as coming from four main contributing causes:

1. MAN, mistakes made by the operator of the equipment;

2. MACHINE, intrinsic imprecision and sources of bias associated with the CI apparatus, including peripherals such as the induction port and pre-separator;

3. ANALYSIS, inadequacies of the chemical assay method for the active pharmaceutical ingredients (APIs);

4. MATERIAL, limitations of the drug product being assessed.

Errors associated with MAN, ANALYSIS and MATERIAL are largely influenced by individual laboratory operating procedures, including operator training and experience (MAN), as well as the physicochemical properties of the formulations associated with the OIP (ANALYSIS and MATERIAL). In addition, operator error (MAN) may also be influenced by the complexity of the measurement device (MACHINE). The reduction in complexity of an AIM over conventional multistage impactors is anticipated as an advantage for this class of devices.

The scope for developing industry-wide best practices for applying the AIM concept is largely confined to the mitigation of errors arising from the MACHINE interface. Such an approach has already led to the identification of so-called Good Cascade Impactor Practices (GCIP) in support of full resolution APSD measurements of OIPs.[9] These provide a starting point for the potential development of a new informative chapter in the United States Pharmacopeia (USP), in support of the current full resolution CI-based compendial methods identified in Chapter <601>.[10]

A similar approach has been used to identify best practices for AIM-based measurements based on the reported experiences of many experimentalists, where implementation of the proposed measure has resulted in an improved correlation with full resolution CI-generated data.

An overriding consideration, as with the selection of any analytical measurement system, is the purpose of the testing (e.g., early development and screening, product characterization, IVIVC, bioequivalence testing, bridging studies, batch release or other). There are several variants of both AIM and full resolution CI-testing. A clear understanding of the purpose of the testing should guide both the selection of device and the approach to CI testing. This topic has been dealt with in some detail by the IPAC-RS Cascade Impactor Working Group.[11]

Figure 2

Fast screening impactor (FSI); an AIM-based apparatus based on the NGI pre-separator design.

Image courtesy of MSP Corporation.

The suggestions summarized in the next section intentionally focus on the laboratory characterization of aerosols from DPIs, since AIM-based methods appear to be increasingly attractive with this category of OIPs.[10] However, many of these practices are applicable to the assessment of other forms of OIPs, such as pressurized metered dose inhalers (pMDIs) with or without add-on spacer/valved holding chambers, soft mist inhalers (SMIs) and nebulizing systems (NEB).

Specific recommendations

1. Select the AIM-based CI system to compare with the appropriate "parent" full resolution CI.

Note on OIP types: Internal dead-space matching is important either where time-of-transport from inhaler to size fractionation zone or volatile evaporation kinetics is an issue; pMDIs/DPIs are therefore most susceptible, but this is likely less important for SMIs and nebulizers.

2. Since the FSI does not have a parent full resolution CI, select this abbreviated im-

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Figure 3

Fine particle dose (FPD) impactor; an AIM apparatus based on the Andersen 8-stage viable impactor.

Image courtesy of Westech Instruments.

Figure 4

Fast screening Andersen (FSA) impactor; an AIM apparatus based on the Andersen 8-stage non-viable impactor.

Image courtesy of Copley Scientific, Limited.

pactor as an aid for fast screening products, but be prepared to experiment to obtain a correlation with the selected full resolution CI.

Note on OIP types: Applicable for all OIP classes; fast screening at pre-formulation may not necessarily require formal correlation with full resolution CI data.

3. The induction port (and pre-separator, if used) should be the same as those used for the reference full resolution CI.

Note on OIP types: Dead-space upstream of the size fractionating zone affects aerosol transport kinetics and evaporation of volatile species; pMDIs/DPIs are therefore most susceptible, but this is likely less important for SMIs and nebulizers.

4. Test at more than one flow rate to establish a range of operation when verifying the correlation between the AIM and full resolution CI, noting that 60 L/min is the standard for DPI testing and many products may be indicated for pediatric users with flow rates significantly < 30 L/min.

Note on OIP types: In vitro performance at several patient-relevant flow rates is the norm in DPI testing to establish aerosol dispersion and transport kinetics in use; pMDI/add-on-device combinations where users may be infants and small children should also be evaluated at flow rates appropriate to end-user indications.

5. Take precautions to minimize the influence of internal dead-space. The magnitude of the internal dead-space in the AIM-based system will likely influence the correlation between size-related metrics from the AIM and their corresponding values obtained with the full resolution "reference" CI.

- Empty stages (no collection surface) can be added with Andersen CI-derived AIM systems to increase dead-space to compensate, thereby improving the stage deposition correlation with the reference full resolution CI;
- If an rNGI is being used, location of the flow output to the flow controller can be chosen (typically below stage 5) to match the time-dependent flow rate profile to that of the full resolution NGI;
- Even when precautions are taken to match dead-space between AIM and full resolution CI systems, it is possible that the overall flow resistances may differ, affecting the correlation. Be prepared to experiment with alternative configurations.

Note on OIP types: Dead-space is likely to affect time-dependent flow rate profile in DPI testing; likely also to influence low-volatile-solvent evaporation kinetics with pMDI solution formulations containing e.g., ethanol as co-solvent; this is unimportant with SMIs and nebulizers.

6. Take advantage of the reduced number of collection sites in an AIM-based apparatus by recovering and assaying for active ingredient(s) after actuating the minimum dose, which is easily quantifiable.

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Figure 5

Deep and standard depth NGI cups; deep cups are used for stages where collection is not required when operating this CI as an AIM-based system.

Image courtesy of MSP Corporation.

Note on OIP types: Fewer API deposition sites result in increased mass loadings; regulatory agencies prefer the number of actuations to reflect indicated dose wherever possible; this is applicable to all OIP classes, especially to high unit API mass per actuation products.

7. Prevent displacement of coating. Even if the collection surfaces of both AIM and full resolution CIs are coated with a tacky substrate to mitigate bias arising from particle bounce and re-entrainment, the kinetic energy of the larger particles arriving at the size-fractionation stage in the AIM-based system may displace the coating altogether. A filter soaked in the coating medium may mitigate the effect.

Note on OIP types: Bounce and re-entrainment are a major source of bias if not controlled; OIPs producing dry particles are more likely to be affected than liquid droplets formed with SMIs and nebulizers.

Statistical considerations

In their simplest form, measures such as impactor-sized mass of active pharmaceutical ingredient, or an appropriate sub-fraction, for example small or fine particle mass, obtained by an AIM apparatus of whatever type can be directly compared to their counterparts derived from full resolution CI analysis for equivalence. Such an approach is likely to involve comparisons based on the 90% confidence interval for paired ratios. However, before such evidence of compatibility of the AIM-based apparatus is presented to a regulatory agency, the reader is counseled to discuss the approach with that agency in order to decide whether such an approach is appropriate for the product concerned and to establish the limits for the 90% confidence interval.

Concluding remarks

AIM systems offer less labor intensive, less time consuming, less complex and therefore less error-prone alternatives to the full resolution impactors. As such, AIM systems should be preferred in those situations where detailed size-band by size-band information may not be necessary, such as in screening of a candidate formulation in early development. Use of good impactor practices, however, is a prerequisite to appropriate use and adoption of AIM. Further, in many circumstances it will be necessary to correlate the results of an AIM with those from a reference full resolution device. IPAC-RS and EPAG are committed to developing and promoting best practices for impactor use. The authors would be interested to hear from users who would like to share their own experiences or recommendations on AIM applications.

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